PB86-134392

Health Effects Assessment for Methylene Chloride

(U.S.) Environmental Protection Agency
Cincinnati, OH

Sep 84

U.S. Department of Commerce
National Technical Information Service
NTIS

PB86-134392

EPA/540/1-86/028
September 1984

HEALTH EFFECTS ASSESSMENT FOR METHYLENE CHLORIDE

U.S. Environmental Protection Agency
Office of Research and Development
Office of Health and Environmental Assessment
Environmental Criteria and Assessment Office
Cincinnati, OH 45268

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Office of Emergency and Remedial Response
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NATIONAL TECHNICAL
INFORMATION SERVICE
U.S. DEPARTMENT OF COMMERCE
SPRINGFIELD, VA. 22161

TECHNICAL REPORT DATA (Please read Instructions on the reverse before completing)		
1. REPORT NO. EPA/540/1-86/028	2.	3. RECIPIENT'S ACCESSION NO. PB86 134392/AS
4. TITLE AND SUBTITLE Health Effects Assessment for Methylene Chloride		5. REPORT DATE September 1984 6. PERFORMING ORGANIZATION CODE EPA/600/22
7. AUTHOR(S)		8. PERFORMING ORGANIZATION REPORT NO.
9. PERFORMING ORGANIZATION NAME AND ADDRESS Environmental Criteria and Assessment Office Office of Research and Development U.S. Environmental Protection Agency Cincinnati, OH 45268		10. PROGRAM ELEMENT NO. 11. CONTRACT/GRANT NO.
12. SPONSORING AGENCY NAME AND ADDRESS Office of Emergency and Remedial Response Office of Solid Waste and Emergency Response U.S. Environmental Protection Agency Washington, DC 20460		13. TYPE OF REPORT AND PERIOD COVERED 14. SPONSORING AGENCY CODE
15. SUPPLEMENTARY NOTES		

16. ABSTRACT

This document represents a brief, quantitatively oriented scientific summary of health effects data. It was developed by the Environmental Criteria and Assessment Office to assist the Office of Emergency and Remedial Response in establishing chemical-specific health-related goals of remedial actions. If applicable, chemical-specific subchronic and chronic toxicity interim acceptable intakes are determined for systemic toxicants, or q_1^* values are determined for carcinogens for both oral and inhalation routes.

A q_1^* was determined for methylene chloride based on inhalation exposure.

q(sub)1 D*

17. KEY WORDS AND DOCUMENT ANALYSIS		
a. DESCRIPTORS	b. IDENTIFIERS/OPEN ENDED TERMS	c. COSATI Field/Group

18. DISTRIBUTION STATEMENT	19. SECURITY CLASS (This Report)	21. NO. OF PAGES
Public	Unclassified	59
	20. SECURITY CLASS (This page) Unclassified	22. PRICE

EPA Form 2220-1 (Rev. 4-77) PREVIOUS EDITION IS OBSOLETE

DISCLAIMER

This report has been funded wholly or in part by the United States Environmental Protection Agency under Contract No. 68-03-3112 to Syracuse Research Corporation. It has been subject to the Agency's peer and administrative review, and it has been approved for publication as an EPA document. Mention of trade names or commercial products does not constitute endorsement or recommendation for use.

PREFACE

This report summarizes and evaluates information relevant to a preliminary interim assessment of adverse health effects associated with methylene chloride. All estimates of acceptable intakes and carcinogenic potency presented in this document should be considered as preliminary and reflect limited resources allocated to this project. Pertinent toxicologic and environmental data were located through on-line literature searches of the Chemical Abstracts, TOXLINE, CANCERLINE and the CHEMFATE/DATALOG data bases. The basic literature searched supporting this document is current up to September, 1984. Secondary sources of information have also been relied upon in the preparation of this report and represent large-scale health assessment efforts that entail extensive peer and Agency review. The following Office of Health and Environmental Assessment (OHEA) sources have been extensively utilized:

U.S. EPA. 1980b. Ambient Water Quality Criteria for Halomethanes. Environmental Criteria and Assessment Office, Cincinnati, OH. EPA 400/5-80-051. NTIS PB 81-117624.

U.S. EPA. 1982. Addenda to Hazard Profiles on Halomethanes. Environmental Criteria and Assessment Office, Cincinnati, OH. Internal draft.

U.S. EPA. 1983b. Reportable Quantity for Dichloromethane. Prepared by the Environmental Criteria and Assessment Office, Cincinnati, OH, for the Office of Solid Waste and Emergency Response, Washington, DC.

U.S. EPA. 1985a. Health Assessment Document for Dichloromethane. Environmental Criteria and Assessment Office, Research Triangle Park, NC. EPA 600/8-82-004F. NTIS PB 85-191559.

U.S. EPA. 1985b Addendum to the Health Assessment Document for Dichloromethane/Methylene Chloride. Updated Carcinogen Assessment of Dichloromethane (Methylene Chloride). External Review Draft. OHEA, Washington, DC. EPA 600/8-82-004FA.

The intent in these assessments is to suggest acceptable exposure levels whenever sufficient data were available. Values were not derived or larger uncertainty factors were employed when the variable data were limited in scope tending to generate conservative (i.e., protective) estimates. Nevertheless, the interim values presented reflect the relative degree of hazard associated with exposure or risk to the chemical(s) addressed.

Whenever possible, two categories of values have been estimated for systemic toxicants (toxicants for which cancer is not the endpoint of concern). The first, the AIS or acceptable intake subchronic, is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs during a limited time interval (i.e., for an interval that does not constitute a significant portion of the lifespan). This type of exposure estimate has not been extensively used or rigorously defined, as previous risk assessment efforts have been primarily directed towards exposures from toxicants in ambient air or water where lifetime exposure is assumed. Animal data used for AIS estimates generally include exposures with durations of 30-90 days. Subchronic human data are rarely available. Reported exposures are usually from chronic occupational exposure situations or from reports of acute accidental exposure.

The AIC, acceptable intake chronic, is similar in concept to the ADI (acceptable daily intake). It is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs for a significant portion of the lifespan [see U.S. EPA (1980a) for a discussion of this concept]. The AIC is route specific and estimates acceptable exposure for a given route with the implicit assumption that exposure by other routes is insignificant.

Composite scores (CSs) for noncarcinogens have also been calculated where data permitted. These values are used for ranking reportable quantities; the methodology for their development is explained in U.S. EPA (1983a).

For compounds for which there is sufficient evidence of carcinogenicity, AIS and AIC values are not derived. For a discussion of risk assessment methodology for carcinogens refer to U.S. EPA (1980a). Since cancer is a process that is not characterized by a threshold, <u>any</u> exposure contributes an increment of risk. Consequently, derivation of AIS and AIC values would be inappropriate. For carcinogens, q_1^*s have been computed based on oral and inhalation data if available.

ABSTRACT

In order to place the risk assessment evaluation in proper context, refer to the preface of this document. The preface outlines limitations applicable to all documents of this series as well as the appropriate interpretation and use of the quantitative estimates presented.

The major issue of concern is the amply demonstrated carcinogenicity of methylene chloride. Human data that rule out carcinogenicity to humans are not available . Animal experiments have clearly demonstrated the carcinogenicity of methylene chloride in mice and strongly suggest carcinogenicity in rats. Methylene chloride has been shown to be mutagenic in Salmonella and to increase the number of chromosomal aberrations in cultured chinese hamster ovary cells. Negative results were obtained for mitotic recombination in yeast, in mutagenicity tests in Drosophila and evaluations of sister chromatid exchange in cultured chinese hamster ovary cells. A human q_1^* of 6.3×10^{-4} $(mg/kg/day)^{-1}$ has been estimated for inhalation exposure from a rat study which showed an increased incidence of salivary gland sarcomas (U.S. EPA, 1985a). An evaluation of the draft results of the NTP (1985) bioassay is currnetly in progress.

ACKNOWLEDGEMENTS

The initial draft of this report was prepared by Syracuse Research Corporation under Contract No. 68-03-3112 for EPA's Environmental Criteria and Assessment Office, Cincinnati, OH. Dr. Christopher DeRosa and Karen Blackburn were the Technical Project Monitors and Helen Ball was the Project Officer. The final documents in this series were prepared for the Office of Emergency and Remedial Response, Washington, DC.

Scientists from the following U.S. EPA offices provided review comments for this document series:

Environmental Criteria and Assessment Office, Cincinnati, OH
Carcinogen Assessment Group
Office of Air Quality Planning and Standards
Office of Solid Waste
Office of Toxic Substances
Office of Drinking Water

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LIST OF ABBREVIATIONS

ADI	Acceptable daily intake
AIC	Acceptable intake chronic
AIS	Acceptable intake subchronic
BCF	Bioconcentration factor
bw	Body weight
CS	Composite score
EKG	Electrocardiograph
LOAEL	Lowest-observed-adverse-effect level
NOEL	No-observed-effect level
ppm	Parts per million
SCE	Sister chromatid exchange
STEL	Short-term exposure limit
TLV	Threshold limit value
TWA	Time-weighted average

1. ENVIRONMENTAL CHEMISTRY AND FATE

The relevant physical and chemical properties and environmental fate of methylene chloride (CAS No. 75-09-2), also known as methylene dichloride and dichloromethane, are shown below.

Chemical class:	halogenated aliphatic hydrocarbon (purgeable halocarbon)
Molecular weight:	84.93
Vapor pressure:	362.4 mm Hg at 20°C (Callahan et al., 1979)
Solubility in water:	13,030 mg/ℓ at 25°C (Horvath, 1982)
Log octanol/water partition coefficient:	1.25 (Callahan et al., 1979)
Soil mobility: (predicted as retardation factor for a soil depth of 140 cm and organic carbon content of 0.087%)	<1.2 (estimated)
BCF:	2.3 (estimated)
Half-life in air:	53-127 days (Singh et al., 1981; Makide and Rowland, 1981)
Half-life in water:	1-6 days (estimated) 30-40 days in lake water (Zoeteman et al., 1980)

The soil mobility value has been estimated from a comparison of the octanol/water partition coefficient values and the solubilities (Callahan et al., 1979) of this compound with those for chloroform and the retardation factor for chloroform given by Wilson et al. (1981).

The estimated half-life value for methylene chloride in water is based on the reaeration rate ratio of 0.650 and oxygen reaeration rate of 0.19-0.96 day^{-1} (Mabey et al., 1981). The difference between this

estimated half-life value and the value given by Zoeteman et al. (1980) for lake water is probably due to the retardation of volatility due to suspended and sedimentated particulated matter in the lake water, a factor not considered in estimating the half-life by the first method.

The BCF for methylene chloride has been estimated from its octanol/water partition coefficient value and the equation given by Veith et al. (1979).

The half-life of methylene chloride in soil could not be located in the literature searched. However, evaporation is expected to be the predominant loss mechanism from the soil surface. In subsurface soil, biodegradation of a chlorinated aliphatic hydrocarbon such as methylene chloride may be slow (Wilson et al., 1983). Therefore, in subsurface soil, the nondegraded methylene chloride is expected to leach into groundwater.

2. ABSORPTION FACTORS IN HUMANS AND EXPERIMENTAL MAMMALS

2.1. ORAL

Pertinent data regarding the absorption of methylene chloride after oral exposure could not be located in the available literature. Roberts and Marshall (1976) indicated that absorption through the intestinal mucosa appeared to be fairly rapid and complete. A number of reports of severe toxicity following ingestion (Llewellyn, 1966; Stewart and Hake, 1976; Friedlander et al., 1978) also imply that absorption following ingestion occurs.

2.2. INHALATION

The majority of data regarding absorption of methylene chloride pertains to inhalation exposure because that route is most likely to be involved in cases of occupational exposure. Several studies in both man and experimental animals have been performed. These data are summarized from U.S. EPA (1981a).

Riley et al. (1966) described the kinetics of absorption and excretion in a 70 kg man exposed for 2 hours to 100 ppm methylene chloride in air. As absorption progressed, the concentration in alveolar air increased, indicating decreased absorption as a steady-state condition was achieved. In this study, equilibrium had not been reached at the end of 2 hours. At this time, exposure was discontinued and methylene chloride in exhaled air was measured. The decline in concentration of methylene chloride in exhaled air appeared to be exponential and roughly proportional to the amount absorbed during the exposure period. The retention factors expressed as a percentage of inhaled dose in this and related studies are summarized in Table 2-1.

TABLE 2-1

Absorption of Methylene Chloride by Human Subjects*
(Sedentary Conditions)

Inhalation Concentration (ppm)	Exposure (hours)	Retention (%)	Reference
50	7.5	70	DiVincenzo and Kaplan, 1981
100	7.5	60	
150	7.5	63	
200	7.5	60	
662	0.30	74	Lehmann and Schmidt-Kehl, 1936
806	0.50	75	
1152	0.50	72	
1181	0.50	70	
44-680	2.00	31	Riley et al., 1966
100	2.00	53	DiVincenzo et al., 1972
100	4.00	41	
200	2.00	51	
250	0.50	55	Astrand et al., 1975
500	0.50	55	
750	1.00	34	Engstrom and Bjurstrom, 1977

*Source: U.S. EPA, 1981a

The theoretical absorption of methylene chloride during short exposures should be related directly to the concentration in inhaled air. Although the protocol that generated these data was not reported by U.S. EPA (1981a), the data of Lehmann and Schmidt-Kehl (1936) confirm this hypothesis.

DiVincenzo and Kaplan (1981) exposed groups of 4-6 volunteers to 50, 100, 150 or 200 ppm methylene chloride for 7.5 hours. Serial breath excretion curves were obtained. Pulmonary absorption was rapid during the first hour, then began to decline as steady-state was approached. Postexposure methylene chloride exposures in exhaled air dropped rapidly. By 7 hours after treatment was terminated, expired air from those volunteers exposed to 50, 100 or 150 ppm contained <0.1 ppm methylene chloride. The concentration in expired air from those exposed to 200 ppm declined to 1 ppm by 16 hours post-treatment. Respiratory elimination consistently accounted for <5% of the total amount of methylene chloride absorbed.

Astrand et al. (1975) stated that the amount absorbed increased with duration of exposure and physical activity (resulting in increased ventilation and cardiac output). Astrand et al. (1975) found that physical activity for 0.5 hours during exposure to 250 or 500 ppm methylene chloride doubled absorption but decreased retention from 55 to 40% because of a 3-fold (6.9-22 ℓ/minute) increase in ventilation rate.

Engstrom and Bjurstrom (1977) demonstrated that methylene chloride absorption was related directly to degree of obesity in human subjects. Obese subjects (fat = 25% bw) absorbed 30% more methylene chloride than lean subjects (fat = 8% bw) when exposed to 750 ppm for 1 hour. Biopsy and analysis of subcutaneous fat revealed a substantial (10.2 and 8.4 mg/kg wet

tissue) concentration in adiposa after 1 and 4 hours postexposure, respectively. Although the concentrations in fat were somewhat lower in obese than in lean subjects, the total amount of body fat resulted in greater total methylene chloride absorption in obese subjects.

Savolainen et al. (1977) exposed rats to air containing 200 ppm methylene chloride 6 hours/day for 5 days. Tissue concentrations were measured in brain, blood, liver and perirenal fat on the 5th day of exposure after 0 (18 hours after exposure on day 4), 2, 3, 4 and 6 hours of exposure. Although no absorption factors were discussed, the persistence in perirenal fat before exposure on the fifth day indicated considerable retention in adiposa relative to other tissues.

3. TOXICITY IN HUMANS AND EXPERIMENTAL ANIMALS

3.1. SUBCHRONIC

3.1.1. Oral. No reports of subchronic oral exposure of humans to methylene chloride have been located in the available literature. Only one study of subchronic oral toxicity of methylene chloride in animals was found. Bornmann and Loeser (1967) exposed 30 male and 30 female Wistar rats for 3 months to drinking water containing 0.125 g methylene chloride/ℓ. Although actual water intake, hence amount of methylene chloride, was not reported in the secondary source (U.S. EPA, 1983b), an intake of 12.5 mg methylene chloride/kg/day was estimated assuming rats weigh 0.35 kg and drink 35 mℓ of water/day. No difference in behavior, appearance, body weight or survival of treatment animals was observed compared with an equal number of control animals. No significant differences in hematologic values, urinalysis or plasma levels of nonesterified fatty acids were found in 8-10 male rats from each group. Blood glucose levels in 10 treated males were slightly elevated compared with 10 control males, but all values fell within the normal range. Estrous cycles, as evaluated by microscopic examination of vaginal smears, indicated no changes that were due to treatment. Necropsy and histopathological examination of ~20 animals of each sex and group revealed no lesions in any internal organ examined. This study defined a free-standing NOEL of 12.5 mg methylene chloride/kg/day in rats whose exposure was from drinking water.

3.1.2. Inhalation. Inhalation exposure of humans to methylene chloride is likely to be a result of occupational exposure; consequently, long-term exposure can be expected. Therefore, studies of repeated exposure of humans to methylene chloride are discussed in Section 3.2.2. Subchronic exposure can be expected in the case of the use of consumer products containing

methylene chloride, such as paint stripping products and various aerosol cans containing the chemical. Historically, subchronic inhalation exposure of humans to methylene chloride has been a concern in one particularly high-risk occupation, astronauts exposed to vapors emanating from materials used in the interiors of spacecrafts. Consequently, several investigators (Thomas et al., 1972; Haun et al., 1971, 1972; Weinstein et al., 1972; MacEwen et al., 1972) exposed laboratory animals to atmospheric methylene chloride for up to 14 weeks. The U.S. EPA (1983b) summarized the results of these studies as follows. Mice exposed to 25 or 100 ppm (87 or 348 mg/m^3) methylene chloride continuously for 14 weeks had an increase in spontaneous activity at the lower concentration but not at the higher one. No gross or histological lesions were found at autopsy, except that livers of the mice exposed to 100 ppm stained positive for fat. Hexobarbital sleep time was unaffected, but hepatic levels of cytochromes were somewhat altered. Rats subjected to the same exposure regimens had nonspecific renal tubular degeneration and regeneration, and hepatic cytoplasmic vacuolization and positive fat staining at both exposure levels. Rats appeared to be the more sensitive species. No specific macro- or microscopic organ changes or changes in hematologic or clinical chemistry values were noted in the small number of monkeys in this study. Carboxyhemoglobin levels, the result of metabolism of methylene chloride to carbon monoxide and subsequent action on hemoglobin, were elevated in monkeys at both exposure levels and in dogs only at the higher exposure, but there was no cumulative increase in carboxyhemoglobin over the period of exposure. No overt signs of toxicity or changes in body weights relative to controls were noted in any of these four species.

Higher levels of continuous exposure were also investigated. Exposure of the same four species to 1000 or 5000 ppm (3480 or 17,400 mg/m^3)

resulted in signs of severe toxicity at the higher dose: narcosis for the first 24 hours and pronounced lethargy for the remainder of the exposure period, reduced food consumption, and high rates of mortality in mice, dogs and monkeys. Rats were somewhat less sensitive; none died. Liver and kidney damage were common findings in all species. At the lower exposure level (1000 ppm), only the dogs were severely affected and died. Mice and rats did not show overt signs of toxicity, but body weight gain was slightly depressed in the rats. Less severe histopathological changes than had been seen at 5000 ppm were noted in the livers of all four species and in the kidneys of rats exposed to 1000 ppm. Monkeys had no significant changes in hematologic or clinical chemistry values.

Taken collectively, these studies seem to indicate that subchronic exposure to methylene chloride causes effects on the liver and kidneys of exposed animals. Lesions in rats exposed to 25 or 100 ppm methylene chloride appear to be more severe than lesions in mice exposed to the same concentrations. Monkeys and dogs seem to be the species least affected. At higher exposure concentrations (1000 ppm), dogs appear to be most sensitive and to experience treatment-related mortality. A level of 25 ppm (87 mg/m^3) in air seems to define a LOAEL in rats when the data from these studies are considered collectively.

3.2. CHRONIC

3.2.1. Oral. No reports of chronic oral exposure of humans to methylene chloride have been found in the available literature. The National Cancer Institute has completed a 2-year study with rats and mice, in which the animals were treated with methylene chloride by gavage. As of May 1985, the study had been withdrawn pending further review.

3.2.2. Inhalation. In humans mild intoxication by methylene chloride results in somnolence, lassitude, anorexia and mild lightheadedness, followed by greater degrees of disturbed central nervous system function and depression. Permanent disability has not been reported. When fatalities occur the cause has been attributed to cardiac injury and heart failure (NAS, 1978).

Further reports of human intoxication from methylene chloride were presented by NIOSH (1976). Most of the case reports were concerned with acute exposure and are not discussed here. Most of the epidemiologic studies lack data on the concentration of methylene chloride in breathing space air or they are complicated by exposure to other chemicals; therefore, they are not suitable for risk assessment.

Weiss (1967) reported a case of toxic encephalosis in a chemist exposed for several hours per day for 5 years to methylene chloride used in a salt-recrystallization operation. Measurements revealed concentrations of 660-3600 ppm methylene chloride in workroom air with a mean of 900 ppm in the breathing zone. This worker had physical contact with liquid methylene chloride.

Recent epidemiological studies have not revealed adverse effects in humans occupationally-exposed to methylene chloride. Friedlander et al. (1978) reported an epidemiological study of male workers at Eastman Kodak exposed primarily to methylene chloride. The workers had been exposed to TWA concentrations of 30-125 ppm methylene chloride (estimated both from air monitoring and blood carboxyhemoglobin levels) for up to 30 years. A proportionate mortality study, using death certificates from 334 exposed workers who died from 1956-1976, was performed. A cohort mortality study involving all 751 workers employed in the exposure area in 1964 and a

separate analysis of a subgroup of 252 of these workers exposed for a minimum of 20 years by 1964 were also performed. Data from this subgroup were analysed separately to discuss effects requiring long latency periods. The follow-up period in the cohort mortality study was 13 years. Control groups consisted of other Eastman Kodak male employees working in production but not exposed to methylene chloride, New York State male cause- and age-specific mortality rates and United States male age-specific mortality rates. Follow-up of workers aged ≥25 years was >97% as of 1964. None of these studies revealed any indication of increased risk of death from circulatory disease including ischemic heart disease, cancer or other causes.

More recently, Ott et al. (1983) investigated mortality and current cardiac health in workers from a fiber production plant in which methylene chloride was used as a solvent. Reasoning that metabolism of methylene chloride to carbon monoxide results in an increase in percentage of carboxyhemoglobin with a commensurate decrease in the oxygen-carrying capacity of the blood, these authors (Ott et al., 1983) suggested that exposure to methylene chloride may lead to an increase in the incidence of ischemic cardiac disease. Data on mortality were obtained from a cohort of workers in a fiber manufacturing plant exposed for at least 3 months between January 1, 1954 and January 1, 1977 to a TWA of ~140 ppm methylene chloride. A control cohort was composed of workers in another part of the plant not exposed to methylene chloride. Another cohort was the expected death data for 5-year intervals matched by race (white and nonwhite) and sex. Mortality data indicated no increase in deaths in either men or women from circulatory system diseases, ischemic heart disease as a separate category, or malignant neoplasms associated with exposure to methylene chloride.

In another study of cardiac function, these investigators (Ott et al., 1983) collected 24-hour EKG data from 50 workers from two fiber producing plants. Data regarding 24 workers from the plant where exposure to TWA concentrations of 60-475 ppm methylene chloride occurred were compared with data from 26 workers from a similar plant not using methylene chloride. No significant changes in ventricular or supraventricular ectopic activity, nor episodic ST segment depression were associated with exposure to methylene chloride.

Burek et al. (1980) briefly discussed other epidemiologic studies (Ott et al., 1980a,b; Skory, 1980; Skory et al., 1980a,b) that apparently revealed no adverse health effects attributable to methylene chloride. The titles of some of these papers indicated that more sensitive parameters of toxicity were evaluated than those studied by Friedlander et al. (1978). Exposure data from these studies were not available in the secondary source from which this discussion was taken (Burek et al., 1980).

Cherry et al. (1981) reported that a group of 46 men occupationally exposed to 75-100 ppm methylene chloride for an unspecified length of time complained of excessive neurological symptoms. Clinical examinations, motor conduction velocity measurements, EKGs and a battery of psychological tests "designed to detect minimal brain damage" were administered to 29 of the exposed men and an equal number of age-matched unexposed men employed at similar jobs. The results revealed no evidence of cardiac abnormalities or neurological or behavioral impairment associated with exposure to methylene chloride.

Burek et al. (1980, 1984) and Dow Chemical Co. (1980) studied chronic inhalation exposure of animals to methylene chloride. Sprague-Dawley rats (SPF-derived, 129/sex/exposure concentration) and Golden Syrian hamsters

(~108/sex/exposure concentration) were exposed to 0, 500, 1500 or 3500 ppm (0, 1740, 5220 or 12,180 mg/m^3) methylene chloride of >99% purity. Exposures were for 6 hours/day, 5 days/week (excepting holidays) for up to 2 years. Rats were subjected to interim kills at 6, 12, 15 or 18 months for cytogenetic or general chemical and histopathological studies.

During the first week of exposure, rats in the high group exhibited a slight decrease in physical activity, but appeared to return to normal activity for the remainder of the trial. During the first 2 months, rats in all groups suffered a disease believed to be sialodacryoadenitis, a transient viral involvement of the salivary glands. No increased mortality was associated with the disease. None of the exposure levels affected body weights, clinical chemistries, or hematologic or urinalysis values in rats. Carboxyhemoglobin levels ranged from 0-5.3% in controls and 8.9-20.4% in exposed rats but did not appear to be dose-related nor related to time of exposure. Mortality was unaffected by treatment except that high-dose females had a significantly elevated mortality rate starting at the 13th month of exposure.

Mean liver weights were increased in both male and female rats in the high-dose group, which was first noticed at the 18-month interim kill. Histopathologically significant alterations related to methylene chloride were found only in the liver. An increased incidence of hepatocellular vacuolization indicative of fatty degeneration was noted in all exposed groups of rats. Incidence and severity appeared to be dose-related. Multinucleated hepatocytes, a spontaneous geriatric change in female rats, were observed after 12 months in exposed and treated groups alike. A significant increase in the number of foci of altered hepatocytes was observed in high-dose females. Males exposed to 1500 or 3500 ppm had an increased incidence

of hepatocellular necrosis and coagulation necrosis. Some females exposed to 500 ppm for 12 months appeared to have slightly increased hepatic hemosiderin. High-dose group female rats and middle- and high-dose male rats had a decreased incidence or severity of chronic progressive glomerulonephropathy, another normal geriatric change, compared with controls. High-dose male rats, consequently, exhibited less severe nonrenal lesions (uremic pneumonitis, mineralization of organs and blood vessels, brain malaria, myocardial degeneration, etc.) associated with chronic progressive renal disease.

In this study hamsters appeared to be less sensitive to methylene chloride than did rats. Although carboxyhemoglobin levels were higher in hamsters (0.3-4.0% in control groups, 22.2-34.6% in treatment groups) than in rats, no clear evidence of toxicity was observed in hamsters. Methylene chloride-exposed hamsters exhibited a decreased incidence or severity of amyloid deposition in their tissues, a normal geriatric change in hamsters, compared with controls.

In rats, this study appeared to define a LOAEL of 500 ppm (1740 mg/m^3), associated with mild hepatomegaly and mild hepatocellular vacuolization indicative of fatty infiltration. Assuming a body weight for rats of 0.35 kg and an inhalation rate of 0.26 m^3/day, exposure for 6 hours/day, 5 days/week resulted in an intake of 230.8 mg/kg/day.

3.3. TERATOGENICITY AND OTHER REPRODUCTIVE EFFECTS

3.3.1. Oral. Pertinent data associating oral exposure of humans to methylene chloride with terata or reproductive effects could not be located in the available literature. The estrous cycle in female rats was reported to be unaffected by exposure to 0.125 g methylene chloride/ℓ in their drinking water for 3 months (Bornmann and Loeser, 1967).

3.3.2. Inhalation. Pertinent data regarding teratogenicity or reproductive dysfunction in humans exposed by inhalation to methylene chloride could not be located in the available literature. Schwetz et al. (1975) exposed Swiss-Webster mice and Sprague-Dawley rats to 1250 ppm (~4350 mg/m³) methylene chloride for 7 hours/day on days 6-15 of gestation. Mouse fetuses were collected and examined on day 18 and rat fetuses were collected and examined on day 21 of gestation. Dams of both species were minimally affected; slightly increased carboxyhemoglobin formation was the only effect reported. Delayed development (manifestations unspecified) was the only effect noted in rat fetuses; in mouse fetuses, slightly advanced ossification of the sternebrae were noted, suggesting accelerated development.

The teratogenic effect of methylene chloride in rats was also investigated by Hardin and Manson (1980). Groups of 26-28 Long-Evans hooded rats were exposed to 4500 ppm (~15,600 mg/m³) methylene chloride for 6 hours/day (group one before and during gestation, group two before gestation and group three during gestation). "Before gestation" exposures were the 3 weeks immediately preceding mating and "during gestation" exposures included the first 17 days of gestation. Gravida from 16-18 dams/group were examined on day 20 of gestation.

A slight but significant decrease in fetal body weight occurred in groups exposed during gestation compared with controls and the group exposed only before gestation. No other abnormalities were reported. Bornschein et al. (1980) reported on the behavioral effects on the pups of 10 dams from each group allowed to deliver. No statistically significant differences in body weight were noted in any of the treatment groups compared with controls, up to 400 days of age. Treatment appeared to have no effects on food and water consumption, wheel running activity or avoidance learning.

The minor and reversible effects on fetal development in mice exposed to 1250 ppm (~4350 mg/m³) methylene chloride reported by Schwetz et al. (1975) appeared to be a LOAEL in this study. Exposure for 7 hours/day, assuming mice inhale 0.05 m³/day and weigh 0.03 kg, resulted in an intake of 2114.6 mg methylene chloride/kg/day. This intake is more than 50 times greater than the intake (26.6 mg/kg/day) in humans associated with occupational exposure to 261 mg/m³ (10 m³ inhaled/day, human body weight of 70 kg) in the study by Cherry et al. (1981). Hence, these data will not impact risk assessment.

3.4. TOXICANT INTERACTIONS

No studies of toxic interactions of methylene chloride with other xenobiotics have been found in the available literature. Some interesting case histories in humans, however, suggest that interactions with other compounds may occur. Functional circulatory disorders in workers exposed for >3 years to methylene chloride and other organochlorine compounds at "permissable" levels have been reported (Dunavskii, 1972). The symptoms, including chest pain, EKG irregularities, bradycardia, decreased myocardial contractility and altered adaptation to physical stress, were not attributed to methylene chloride alone.

The metabolism of methylene chloride to carbon monoxide forms the basis for concern about combined exposure to methylene chloride and carbon monoxide. Fodor and Roscovanu (1976) reported that exposure of human subjects to 500 ppm of methylene chloride (for an unspecified duration) resulted in levels of carboxyhemoglobin in blood comparable with those produced by the TLV for carbon monoxide, 50 ppm. Mixed exposures could pose a serious threat to the well being of occupationally-exposed workers, smokers or cardiorespiratory patients.

Savolainen et al. (1977) expressed concern about exposure to methylene choride and other lypophilic solvents resulting in enhanced danger of marked central nervous system and metabolic effects.

Christenson and Huizinga (1971) reported the case of a 17-year-old male found dead in a turret where he had been using a mixture of 80% methylene chloride and 14.9% methanol to remove paint. Barbiturate derivatives were found in the blood, brain, urine and stomach contents. Death was ascribed to the combination of methylene chloride and barbiturates. This report suggested the ability of barbiturates to potentiate the toxicity of methylene chloride.

Finally, two reports of phosgene poisoning related to methylene chloride (Gerritsen and Buschmann, 1960; English, 1964) point out that phosgene, a combustion product of methylene chloride, is highly toxic. Both cases involved the use of methylene chloride as a paint remover in an enclosed area heated with a portable kerosene heater. One case (Gerritsen and Buschmann, 1960) involved a woman who was exposed for a 3-hour period during 1 day when she was 7 months pregnant; that evening, she expectorated blood-tinged sputum and felt a tightness in her chest. The next day she was hospitalized with dyspnea, cyanosis, and elevated pulse and body temperature. She was treated and discharged 8 days later. She gave birth to a healthy infant 2 months later.

The second case (English, 1964) involved a 67-year-old interior decorator exposed for 8 hours to methylene chloride in a small unventilated room heated with a portable kerosene heater. He experienced breathlessness, headache, giddiness and a tightness across the chest. Upon hospitalization the next day he was cyanotic, sweating, and tachypneic with extensive coarse rales in both lungs. He was discharged after 5 weeks but experienced lassitude, weakness and hypochondriosis for an additional 3 months.

4. CARCINOGENICITY

4.1. HUMAN DATA

Pertinent data regarding the carcinogenicity in humans associated with methylene chloride could not be located in the available literature.

4.2. BIOASSAYS

4.2.1. Oral. An NCI bioassay of methylene chloride has been conducted on rats and mice, exposed by gavage, but as of May, 1985, the study had been withdrawn pending further review.

The National Coffee Association performed a 24-month toxicity and carcinogenicity bioassay in F344 rats (NCA, 1982a,b) and B6C3F1 mice (NCA, 1983). In the rat study, groups of 85 males and 85 females were administered drinking water that provided methylene chloride at 0, 5, 50, 125 or 250 mg/kg bw/day for 24 months. A second control group of 50 rats/sex and a high dose group (250 mg/kg bw/day) of 25 rats/sex were added to undergo treatment for 78 weeks followed by a 26-week recovery period. The only tumor that occurred at increased incidences was combined neoplastic nodules and hepatocellular carcinoma in female rats ($p>0.05$). These incidences (0/134, 1/85, 4/83, 1/85, 6/85 in combined control, 5, 50, 125 and 250 mg/kg bw/day groups, respectively), however, were within those observed in theoretical controls and the U.S. EPA (1985a) concluded that methylene chloride showed "borderline" carcinogenicity in F344 rats.

In the mouse experiment, groups of 50 females and 60-200 males were treated with drinking water that provided 0, 60, 125, 185 or 250 mg methylene chloride/kg bw/day for 24 months. A marginally significant ($p<0.05$) increase in the combined incidence of hepatocellular adenoma and carcinoma was recorded in male mice (24/125, 51/200, 30/100, 31/99 and 35/125 in combined control, 60, 125, 185 and 250 mg/kg bw/day groups, respectively).

The U.S. EPA (1985a) considered the evidence for the carcinogenicity of methylene chloride in mice to be "borderline".

4.2.2. Inhalation. Burek et al. (1980, 1984) and Dow Chemical Co. (1980) studied the carcinogenicity of methylene chloride from chronic (2-year) inhalation exposure. Sprague-Dawley rats and golden Syrian hamsters were exposed to methylene chloride at 0, 500, 1500 or 3500 ppm for 6 hours/day, 5 days/week for up to 2 years. As was mentioned previously, hamsters seemed to be less sensitive to the systemic toxic effects of methylene chloride than were rats. No exposure-related differences in the incidences of benign or malignant tumors were observed in male hamsters. There was a statistically significant increase in the incidence of benign tumors in female hamsters exposed to 3500 ppm methylene choride, but this increase was attributed to increased longevity enjoyed by that group as a result of delayed diseases of aging.

In female rats, an increase in the number of benign mammary tumors per tumor-bearing rat (but not in the number of tumor-bearing rats) was observed at all dose levels. An increase in the number of benign mammary tumors in tumor-bearing rats was also noted in males in the high-dose group. More importantly, a dose-related increase in sarcomas involving the salivary gland became statistically significant at the high-dose exposure level in male rats (Table 4-1). These tumors appeared to arise from mesenchymal rather than epithelial tissue. Interpretation of these findings is difficult, according to the investigators (Burek et al., 1984). Studies of chronic methylene chloride exposure at high levels in a wide variety of laboratory species have established the liver as the primary target organ.

TABLE 4-1

Summary of Salivary Gland Region Sarcoma Incidence in Male Rats in a 2-Year Inhalation Study with Dichloromethane[a]

Dose (ppm)	Incidence[b]	Fisher's Exact Test
0	1/93 (1%)	NA
500	0/94 (0%)	NA
1500	5/91 (5.5%)	(p=0.10, NS)
3500	11/88 (12.5%)	(p=0.002)

[a]Source: Burek et al., 1980, 1984; Dow Chemical Co., 1980

[b]Cochran-Armitage test for linear trend, $p<0.0001$.

NS = Not significant; NA = not applicable

The present indication of an apparent relationship between methylene chloride and the salivary gland was unusual and appeared to be inconsistent with previously reported data. Early in the course of treatment, these rats had apparently contracted a viral disease, sialodacryoadenitis, in the salivary glands. It was suggested that the combination of the virus with methylene chloride may have increased the incidence of salivary gland neoplasia. The fact that these sarcomas appeared to arise from mesenchymal tissue rather than from epithelial (glandular) tissue added to the confusion. The authors (Burek et al., 1984) expected primary salivary gland neoplasms to arise from epithelial cells.

More recently, Dow Chemical Co. (1982) conducted a 2-year inhalation toxicity and oncogenicity study in rats exposed to 0, 50, 200 or 500 ppm, 6 hours/day, 5 days/week for 20 (males) or 24 months (females). Interim necropsies were performed at 6, 13, 15 and 18 months. No treatment-related increase in tumor incidence was observed. This study has been criticized for using doses too low to elicit a positive response. Consequently, the National Toxicology Program has performed another inhalation study in rats and mice (NTP, 1985). The board draft of this study has been released in an unaudited form. In this experiment, 50 male and 50 female F344/N rats were exposed to air containing 0 (chamber controls), 1000, 2000 or 4000 ppm, 6 hours/day, 5 days/week for 102 weeks. Concurrently, 50 male and 50 female B6C3F1 mice were exposed by the same schedule to air containing 0, 2000 or 4000 ppm methylene chloride. During week 3 of treatment, rats of both sexes in the 1000 ppm group were exposed to 2000 ppm and rats of both sexes in the 2000 ppm group were exposed to 1000 ppm.

In rats, a significant positive trend ($p<0.001$) for mammary tumors (fibroadenoma, adenoma, fibroma: combined incidence) was observed in both

sexes (Table 4-2). The incidence in high group males and females was significantly greater than in control rats ($p<0.001$). Similarly, the incidence of subcutaneous fibroma or sarcoma (combined) in male rats was higher in high group males than controls ($p<0.05$) and a positive trend ($p=0.008$) was observed. The incidence of these tumors was combined because they all occurred in the mammary chain and were considered to be of the same etiologic origin. Other tumor types also occurred with a significant positive trend by life table analysis, but were not significant in treated vs. control groups. These included the combined incidence of neoplastic nodules and hepatocellular carcinomas in female rats, adrenal gland pheochromocytoma and interstitial cell tumors in males, squamous cell metaplasia in females, pituitary gland adenoma or carcinoma and mononuclear cell leukemias in both sexes. In male rats, the incidence of mesothelioma derived from the tunica vaginalis was found to be significantly higher in both the high and intermediate groups than in controls, but the incidence in controls in this experiment was unusually low compared to historical controls.

The most striking observation in the mice was the incidence of lung tumors ($p=0.0001$) in treated mice (Table 4-3). The period of latency was significantly reduced in treated mice and lung tumors were believed to be responsible for the reduced survival observed in high-dose group males and females. Also noteworthy was the incidence of liver tumors in treated mice (see Table 4-3).

4.3. OTHER RELEVANT DATA

The available literature contains sufficient information on the mutagenicity of methylene chloride; several experiments are summarized in Table 4-4. Simmon et al. (1977) reported that methylene chloride was mutagenic to Salmonella typhimurium strain TA100 when assayed in a dessicator whose atmosphere contained the test compound. Metabolic activation was not required.

TABLE 4-2

Tumor Incidence in Rats Treated with Methylene Chloride[a]

Tumor Type	Control	1000 ppm	2000 ppm	4000 ppm
MALES				
Fibroadenoma, adenoma, fibroma of mammary gland	0/50	0/50	2/50	5/50[b]
Subcutaneous (combined) tumors of mammary area	1/50	1/50	4/50	9/50[c]
FEMALES				
Fibroadenoma, adenoma, fibroma of mammary gland	7/50	13/50	14/50	23/50[b]

[a]Source: NTP, 1985

[b]$p<0.001$

[c]$p=0.002$

TABLE 4-3

Tumor Incidence in Mice Treated with Methylene Chloride[a]

Tumor Type	Control	2000 ppm	4000 ppm
MALES			
Alveolar/bronchiolar adenomas	3/50	19/50	24/50[b]
Alveolar/bronchiolar carcinomas	2/50	10/50	28/50[b]
Multiple lung tumors	0/50	10/50	28/50
Hepatocellular adenoma and carcinoma	22/50	24/49	33/49[c]
Hepatocellular carcinoma	13/50	15/49	26/49[d]
Multiple liver tumors	2/50	11/49	16/46
FEMALES			
Alveolar/bronchiolar adenomas	2/50	23/48	28/48[b]
Alveolar/bronchiolar carcinomas	1/50	13/48	29/48[b]
Multiple lung tumors	0/50	11/48	29/48
Hepatocellular adenoma and carcinoma	2/50	6/48	22/48[e]
Hepatocellular carcinoma	1/50	11/48	32/48[e]
Multiple liver tumors	0/50	3/48	28/48

[a]Source NTP, 1985

[b]$p=0.0001$

[c]$p=0.016$

[d]$p=0.005$

TABLE 4-4

Mutagenicity and Genotoxicity of Methylene Chloride*

Assay	Indicator Organism	Application	Concentration or Dose	Activating System	Response	Comments	Reference
Reverse mutation	Salmonella typhimurium TA1535, TA1537, TA1538, TA98, TA100	vapor exposure	0-800 µl/9 l dessicator	±S-9	+ – +	Data reported only for TA100; positive with or without S-9 activation	Simmon et al., 1977
Reverse mutation	S. typhimurium TA100	vapor exposure	0-1 ml/9 l dessicator	±S-9	+ +	S-9 may enhance, but not required for mutagenicity	Simmon and Kauhanen, 1978
Reverse mutation	S. typhimurium TA1535, TA100	vapor exposure	0-8.3% in air	±S-9	+ +	S-9 enhanced mutagenicity; dose-response was evident in TA100	Green, 1983
Reverse mutation	S. typhimurium TA1535	vapor exposure	0-10% theoretical in air	none	+	Clear-cut dose-response clearly evident	McGregor, 1979
Reverse mutation	S. typhimurium TA1535, TA1537, TA1538, TA98, TA100	vapor exposure	NR	+S-9	+ –	Positive result only when conducted in gas tight chamber	Mestmann et al., 1980
Reverse mutation	S. typhimurium TA98, TA100	vapor exposure	0-1 ml/ chamber	±S-9	+ +	Positive in both TA98, TA100	Snow et al., 1979
Reverse mutation	S. typhimurium TA98, TA100	NR	NR	S-9	+	Data available in abstract form only	Kanada and Uyeta, 1978
Reverse mutation	S. typhimurium TA98, TA100	vapor exposure	0-57,000 ppm	±S-9	+ +	Response positive and dose-related	Jongen et al., 1978
Reverse mutation	S. typhimurium TA1535, TA98, TA100	vapor exposure	0-10,000 ppm		+ +	Positive dose-related response only in air tight chamber	Barber et al., 1981
Reverse mutation	S. typhimurium TA100	vapor exposure	0-8.4%	±S-9	+ +	Positive dose-related response, S-9 activation did not enhance response	Green, 1981
Reverse mutation	S. typhimurium TA1535, TA1537, TA1538, TA98, TA100	vapor exposure	0-750 ml/ dessicator	±S-9	+ +	Weak positive response	Gocke et al., 1981
Reverse mutation	S. typhimurium TA100	vapor exposure	0-1.4%	±S-9, cytosal, microsomes	+ +	Activation with cytosol yielded maximum response	Jongen et al., 1982

TABLE 4-4 (cont.)

Assay	Indicator Organism	Application	Concentration or Dose	Activating System	Response	Comments	Reference
Rec assay	Bacillus subtilis	NR	NR	NR	-	Data available only in abstract form	Kanada and Uyeta, 1978
Mitotic recombination	Saccharomyces cerevisiae D7	NR	0-209 mM	NA	+	D7 strain metabolizes methylene chloride to active intermediates	Callen et al., 1980
Mitotic recombination	S. cerevisiae D3	NR	NR	NR	-	Minimal data presented	Simmon et al., 1977
Sex-linked recessive lethal	Drosophila	fed or injected	NR	NA	-	Votalization not prevented	Abrahamson and Valencia, 1980
Sex-linked recessive lethal	Drosophila	fed	0-620 mM	NA	+	Conclusion; methylene chloride is mutagenic to sperm	Gocke et al., 1981
Sex-linked recessive lethal	Panagrelus redivivus	NR	10^{-6} to 10^{4} mol/L	NA	+	Equivocal positive results	Samoiloff et al., 1980
Mutations in cell-culture	CHO and V79 cells	cell culture	0-5%	NA	-	Equivocal negative results	Jongen et al., 1981
Chromosomal aberration	rat bone marrow cells	inhalation	0-3500 ppm	NA	-	NC	Dow Chemical Co., 1980
Chromosomal abberation	CHO cells	cell culture	0-10 µL/mL	NA	+	Similar results in three replications	Thilagar and Kumaroo, 1983
Chromosomal aberration	NMRI mice/bone marrow	i.p. injection	0-3400 mg/kg bw	NA	+ -	Results equivocal	Gocke et al., 1981
Sister-chromatid exchange	SCE/V79 cells	cell culture	0-4.0%	NA	+	Positive dose-response	Jongen et al., 1981
Sister-chromatid exchange	CHO cells	cell culture	0-10 µL/mL	NA	+ -	Marginal but not significant response	Thilagar and Kumaroo, 1983

*Compound and/or purity not reported

NR = Not reported; NA = not applicable; NC = no comment

The response was strongly dose-related. This is typical of the response of many strains of S. typhimurium to methylene chloride (see Table 4-4). In S. cerevisiae D3, however, mitotic recombination was not increased by methylene chloride (Simmon et al., 1977) although positive results were obtained in S. cerevisiae D7 (Callen et al., 1980). Additionally, Filippova et al. (1967) reported that methylene chloride was negative when tested for sex-linked recessive lethals in Drosophila melanogaster although positive results were obtained by Gocke et al. (1981).

Thilagar and Kumaroo (1983) investigated the ability of methylene chloride to induce SCE and chromosomal aberrations in cultured Chinese hamster ovary cells. They observed extensive chromosomal aberrations, both with and without Aroclor 1242- and 1254-induced rat S-9 fraction activation. Negative results were reported in the SCE assay. These authors discovered that running the tests in plastic rather than glass markedly reduced the magnitude of the positive response, indicating the likely adsorption of methylene chloride to the plastic.

4.4. WEIGHT OF EVIDENCE

Pertinent data regarding carcinogenicity in humans associated with methylene chloride could not be located in the available literature. Although an NCI bioassay has been conducted in rats and mice using gavage administration, the data are not yet available. Burek et al. (1980, 1984) demonstrated that sarcomas of the salivary gland in male rats are associated with inhalation exposure to high levels (3500 ppm) of methylene chloride. Interpretation of the biological significance of these results is rendered difficult for the reasons discussed in Section 4.2. Another NCI bioassay involving inhalation exposure has recently been performed (NTP, 1985). The results indicate that methylene chloride is probably carcinogenic to rats (mammary tumors) and clearly carcinogenic to mice (lung and liver tumors).

Applying the criteria for evaluating the overall weight of evidence of carcinogenicity to humans proposed by the Carcinogen Assessment Group of the U.S. EPA (Federal Register, 1984), methylene chloride is most appropriately classified a B2 - Probable Human Carcinogen.

5. REGULATORY STANDARDS AND CRITERIA

Pertinent regulatory standards and criteria for methylene chloride are summarized in Table 5-1. According to the ACGIH (1981) the TLV committee adopted a criteria of 500 ppm in the industrial workplace. Subsequent discoveries that exposures approaching this magnitude resulted in substantially elevated blood levels of carboxyhemoglobin led to a modification of the TLV to 100 ppm; a STEL of 500 ppm has been proposed. In 1983, the ACGIH (1983) had recommended reducing the STEL to 350 ppm.

The NIOSH (1976) criteria for methylene chloride was set at a TWA of 75 ppm for a 10-hour workday, 40-hour workweek. Recognizing the relationship between methylene chloride and carbon monoxide, a formula has been derived to deal with methylene chloride when carbon monoxide concentrations are >9 ppm. The formula is $[C(CO) \div L(CO)] + [C(DCM) \div L(DCM)] < 1$ where:

C(CO) = TWA concentration of carbon monoxide ppm

L(CO) = 35 ppm, the recommended TWA limit for carbon monoxide

C(DCM) = TWA concentration of methylene chloride, ppm

L(DCM) = 75 ppm, the recommended TWA limit for methylene chloride.

As an oil and fat solvent, methylene chloride is allowed in spice oleoresins at concentrations up to 30 mg/kg and in decaffeinated coffee at concentrations up to 10 mg/kg, according to NIOSH (1976).

OSHA (1976) has established occupational exposure standards as follows: 8-hour TWA, 1737 mg/m^3; acceptable ceiling concentration, 3474 mg/m^3; acceptable maximum peak > ceiling (5 minutes in any 3 hours), 6948 mg/m^3.

The U.S. EPA (1980b) has set the ambient water quality criterion at 6 µg/ℓ on the basis of qualitative but not quantitative data concerning the carcinogenicity of methylene chloride. They felt that the median concentration found in ambient water should not be exceeded until more definitive data quantifying cancer risk to oral exposure have been generated.

TABLE 5-1

Regulatory Standards or Criteria for Methylene Chloride

Standard or Criteria	Value	Reference
TLV STEL	100 ppm (~360 mg/m³) 500 ppm (~1700 mg/m³)	ACGIH, 1981
TWA*	75 ppm	NIOSH, 1976
TLV STEL	100 ppm 350 ppm	ACGIH, 1983
Level in spice oleo-resins	30 mg/kg	NIOSH, 1976
Level in decaffeinated coffee	10 mg/kg	
8-hour TWA Acceptable ceiling Maximum peak	1737 mg/m³ 3474 mg/m³ 6948 mg/m³	OSHA, 1976
Ambient water quality criterion	6 µg/ℓ	U.S. EPA, 1980
1-Day SNARL 10-Day SNARL Longer SNARL	13 mg/ℓ 1.3 mg/ℓ 0.15 mg/ℓ	U.S. EPA, 1981b

*See discussion in text for concurrent exposure to carbon monoxide.

Based on data from acute and subacute toxicity studies, the Office of Drinking Water Advisory Opinion for methylene chloride (U.S. EPA, 1981b) has made Suggested No Adverse Response Level (SNARL) recommendations for methylene chloride as follows: 1-day exposure, 13 mg/ℓ; 10-day exposure, 1.3 mg/ℓ; and for longer exposures, 0.15 mg/ℓ.

6. RISK ASSESSMENT

6.1. ACCEPTABLE INTAKE SUBCHRONIC (AIS)

Methylene chloride has been demonstrated to be carcinogenic in both rats and mice. Data are sufficient for estimating carcinogenic potency; therefore, it is inappropriate to derive an AIS for this chemical.

6.2. ACCEPTABLE INTAKE CHRONIC (AIC)

Methylene chloride has been demonstrated to be carcinogenic in both rats and mice. Data are sufficient for estimating carcinogenic potency; therefore, it is inappropriate to derive an AIC for this chemical.

6.3. CARCINOGENIC POTENCY (q_1^*)

6.3.1. Oral. The NCI has performed an oral exposure bioassay of methylene chloride in rats and mice. These data are not available, as this study has been withdrawn pending further audit.

The U.S. EPA (1985a) reviewed an oral bioassay conducted by the National Coffee Association (NCA, 1982a,b). This study provided suggestive evidence of a treatment-associated increased incidence of hepatocellular carcinomas/adenomas in male mice. In female rats the incidence of neoplastic nodules/hepatocellular carcinomas was increased with respect to matched but not historical controls. U.S. EPA (1985a) felt this study was inadequate for quantitative risk assessment.

6.3.2. Inhalation. The study by Burek et al. (1980, 1984) associated the incidence of salivary gland sarcomas in male rats with exposure to methylene chloride (see Sections 3.2. and 4.2.). The incidence of tumors (control, 1/124; 500 ppm, 0/124; 1500 ppm, 5/124; 3500 ppm, 11/124) was significantly different from matched controls at the highest dosage level. The Cancer Assessment Group (U.S. EPA, 1985a) has used these data to calculate a human q_1^* of 6.3×10^{-4} $(mg/kg/day)^{-1}$.

More recently, the results of the NTP (1985) bioassay have become available in draft form. The U.S. EPA (1985b) is in the process of reevaluating the carcinogenicity of methylene chloride in the context of these more recent results. However, an assessment in final quotable form is still pending.

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APPENDIX

Summary Table for Methylene Chloride

Carcinogenic Potency	Species/Sex	Experimental Dose/Exposure	Effect	q_1^*	Reference
Inhalation	rats	12,159 mg/m³ 6 hours/day, 5 days/week for 2 years	salivary gland sarcomas carcinoma	6.3×10^{-4} $(mg/kg/day)^{-1}$	Burk et al., 1980, 1984
Oral	NA	NA	NA	ND	NA

NA = Not available

ND = Not derived